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FDA Draft Guidance for Industry: Clinical Considerations for Therapeutic Cancer Vaccines (published September 18, 2009)

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Comment by the Regulatory Research Party of the Cancer Immunotherapy Consortium (CIMT)

The CIMT Regulatory Research Party (RRP) has discussed the FDA draft guidance at its last meeting which took place in Mainz (Germany) on November 18, 2009. This comment is also supported by the Executive Board of the Cancer Immunotherapy Consortium (CIMT) and the CIMT Immunoguiding Program (CIP) workgroup.

General comment

The RRP acknowledges the high quality and deep knowledge and understanding of cancer vaccines reflected in the draft guidance and considers the document as a very important and valuable guidance for the early- and late-stage clinical development of therapeutic cancer vaccines for industry and academia. This particularly relates to:

- conducting clinical trials with cancer vaccines also in patients with no evidence of residual disease or minimal disease burden,
- the acknowledgement of a delayed onset of a clinical activity and its implications on the vaccination protocol and trial design,
- the potential continuation of vaccination beyond progressive disease under certain conditions and
- the importance of monitoring the immune response.

The RRP would like to specifically comment on following sections:

Section II. – Background

These APCs then present antigenic determinants in a Human Leukocyte Antigen (HLA) - restricted fashion to T cells ~~and/or B cells~~, which in turn can attack tumor cells that express cognate antigenic determinants or can provide help for B cell responses that produce antibodies, which in some cases could lead to tumor cell death.

In line 5 “and/or B cells” should be deleted. According to our knowledge APCs present antigens in a HLA-restricted manner only to T cells but not to B cells.

The course of antigen presentation and processing, activation of lymphocytes, and tumor cell killing, is expected to require a considerable time in vivo~~, especially if vaccination requires several doses~~.

In line 9 it is proposed to delete “especially if vaccination requires several doses”. According to our knowledge, there is no relationship between repeated vaccine administration and delayed biological effect. On the contrary, repeated administration would be rather thought to shorten the time to onset to a clinically meaningful T-cell response.

Section III. A. 1. – Patient population

The RRP welcomes that besides the metastatic setting also patients with minimal disease burden or even no evidence of residual disease should be considered for cancer vaccination trials.
However, it also seems important to inform such patients, that single randomized trials with certain cancer vaccines in melanoma patients (Morton et al., 2007; Eggermont et al., 2008) have indicated to induce tolerance with a potential negative impact on recurrence-free and/or overall survival. Such observations are so far not conclusive, certainly cannot be generalized and require further studies until a more definite conclusion can be reached. Thus, the RRP recommends monitoring potential mechanisms of tolerance induction in cancer vaccine-treated patients wherever possible to further contribute to the elucidation of this question. See below comment to monitoring of immune response.

Section III. A. 2. – Monitoring of immune response

The CIMT Immunoguiding Program (CIP) Workgroup and the RRP considers immune monitoring as mainly descriptive especially in early-stage trials with the major goal to establish a proof-of-principle for the proposed pharmacological effect and to show immunogenicity of the administered antigens. Requirements regarding the number of assays, level of qualification/validation of assays and pre-specification of assays are dependent on the stage of development and the endpoints of the trials.

Number of immune assays:
While it is strongly desirable to have at least two different immunological assays able to sustain the test results, it may be sufficient to apply one assay at an early stage of development because at this stage immunomonitoring would simply serve the purpose to show that a vaccine is immunogenic. Preferably, immunomonitoring at this stage also focuses on the measurement of responses against multiple epitopes within the vaccine to get insight into the breadth of an immune response (Kenter et al., 2009). In phase II trials a set of complementary assays could be used for full determination of the vaccine-induced immune response and to identify assays correlating with clinical efficacy.

Level of qualification/validation:
At an early stage of clinical development, it may be sufficient to use immune assays that have undergone either
- a limited level of qualification, i.e. the use of SOPs for assay performance and analysis, auditing of all final results and use of only well trained personnel (per lab SOP) or
- harmonization within external quality assurance programs (e.g. proficiency panels),
as recommended by the CIMT Immunoguiding Program and the Cancer Research Institute's Cancer Vaccine Consortium (Britten et al., 2009).
A full validation of one or more (immune-correlating) assays should be performed before entering phase III clinical trials. Naturally, if the immune assay is used for decision of patient treatment, a full validation is absolutely necessary.

Pre-specification of assays in first-in-man trials:
For first-in-man trials where novel antigens are tested for the first time and the level of immunogenicity of the antigens is not known, it may be considered to determine the final

assays, assay parameters and assay conditions to be used in this trial once the samples from the first patients (e.g. N=6) have been tested. After review of this data, the assays and assay specifications may need to be revised. Such a procedure could be pre-specified in the clinical protocol.

Assays to potentially monitor immune tolerance:
Wherever possible, tests should be developed that measure potential mechanisms of immune tolerance induction by cancer vaccines. Levels of cellular (e.g. regulatory T cells, myeloid suppressor cells, IL-17 secreting T cells etc.) and serum biomarkers should be monitored wherever possible. Such a measurement is purely descriptive and hypothesis-generating, as it is currently unknown whether induction of tolerance can be predicted by such assays. Once such hypotheses are generated, they require validation in subsequent trials.

Section III. A. 3. – Disease progression/recurrence immediately or shortly after the initial administration of cancer vaccines

The RRP welcomes the consideration that cancer patients may be vaccinated beyond initial disease progression or recurrence under certain conditions. In addition to the proposed conditions the RRP strongly recommends to install a board of independent experts (typically a data safety monitoring board – DSMB) that frequently reviews decisions to continue vaccinations of such patients according to a number of pre-specified parameters and decide on the further vaccination and duration of further vaccination.

Due to the delayed effect of therapeutic cancer vaccines and a late separation of progression-free and/or overall survival curves, the RRP suggests emphasizing the point, that a sufficiently long follow-up period for the clinical endpoints – especially for overall survival – should be implemented in the protocol. It is also possible, that a cancer vaccine “sensitizes” a tumor to respond more strongly to a subsequent cytotoxic, targeted or other cancer therapy (Schlom et al. 2007). Thus, also the nature and duration of subsequent therapies should be followed and documented.

Section III. B. 2. – Dose escalation

The RRP acknowledges the necessity of dose escalation particularly with novel classes of agents. For classes of agents that have been tested extensively in clinical trials and have sufficiently demonstrated that there is no maximum tolerated dose, it may be considered to conduct the trial at only one dose level if the relevance of existing clinical data is submitted by the sponsor.
For autologous cancer vaccines where the vaccination material is usually limited, a dose escalation may not be feasible for the autologous component of the vaccine.

References

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Information on the authors

The Cancer Immunotherapy (CIMT) consortium is a non-profit organization and was founded in fall 2002 as an information and education platform for immunological cancer therapy. CIMT organizes annual scientific meetings located in Mainz, Germany. The CIMT Regulatory Research Party (RRP) was founded in 2008. It incorporates members from academia, biotech industry and regulatory authorities such as the Paul-Ehrlich-Institute (PEI). The group is aiming to facilitate the translation of scientific knowledge from bench to bedside. RRP's main goals are: (1) identification of regulatory challenges posed by emerging immunotherapies, (2) development of new regulatory concepts to facilitate clinical testing of innovative immunotherapies and (3) to facilitate discussion between all groups relevant for the translation of scientific knowledge into the hospital. The RRP is chaired by Prof. Ulrich Kalinke, director of the TwinCore Institute (Hannover, Germany) and former Head of Immunology at the Paul-Ehrlich-Institute, the German regulatory authority for the approval of biological drugs. (http://cimtmainz.org).